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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/838,987	04/20/2001	Ronald S. Chamberlain	2026-4231US3	2855

23460 7590 04/19/2004

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EXAMINER	
WILSON, MICHAEL C	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 04/19/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/838,987	CHAMBERLAIN ET AL.	
	Examiner	Art Unit	
	Michael C. Wilson	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 January 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8,21 and 22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,21 and 22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 2-23-04 has been entered.

The amendment filed 1-8-04 has been entered as requested. Applicant's arguments filed 1-8-04 have been fully considered but they are not persuasive. Claims 1-8, 21 and 22 remain pending in the instant application. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Objections

In claim 1, "at least one antigen" in the preamble should be "an antigen" to reflect the body of the claim.

In claim 1, the phrase "against which an immune response is to be induced" in (i) and lines 3-4 of (ii) is confusing. The claim clearly sets for that an immune response against the antigen is induced in the mammal in the last two lines.

In claim 1, the grammar of the steps is not parallel. The steps of "inoculating" the mammal with a first and second vector should result in "inducing" an immune response

in the mammal. The phrase "thereby inducing an immune response against said antigen in the mammal" would overcome this objection.

In claim 5, the language is wordy and confusing. The phrase is intended to describe the nucleic acid insert but uses the phrase "of the first and second recombinant vectors encoding said antigen". The phrase "wherein the nucleic acid inserts of the first and second recombinant vectors further comprise a nucleic acid sequence encoding...." Please note: the "nucleic acid encoding an immunostimulatory protein" should be a "nucleic acid sequence encoding...." The phrase "against which an immune response is to be induced" should be deleted for clarity.

In claims 21 and 22, the language is wordy and confusing. Now that claim 1 has been amended to clearly set forth that the antigen in the first vector is the same as the antigen in the second vector, claims 21 and 22 can be simplified. All that is required in claims 21 and 22 is reference to "said antigen" which must be the same in both vectors of claim 1. E.g. "wherein said antigen is a tumor-associated antigen" in claim 21 would refer to the antigen that is identical in both the first and second vector of claim 1.

Claim Rejections - 35 USC ' 112

1. Claims 1-8, 21 and 22 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inducing a CTL response in a mammal comprising administering a vaccinia viral vector encoding

an antigen operably linked to a promoter followed by administering a fowlpox vector encoding said antigen operably linked to a promoter such that an increased CTL response against said antigen occurs as compared to vaccinia followed by vaccinia (both encoding the antigen), fowlpox followed by fowlpox (both encoding the antigen) or fowlpox followed by vaccinia (both encoding the antigen), does not reasonably provide enablement for inducing a therapeutic or prophylactic immune response against an antigen using the claimed invention. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims for reasons of record.

While the claims do not require inducing a therapeutic or prophylactic immune response against an antigen, inducing a therapeutic or prophylactic immune response against an antigen is the only disclosed use for inducing an immune response in a mammal. The specification teaches inducing an immune response against β-gal to find methods of vaccination that generate a CTL or antibody response that is therapeutic or prophylactic (pg 4, lines 2-13) and inducing an immune response against cancer (original claim 9). Therefore, the claims are being considered under enablement for their only disclosed use, i.e. inducing a therapeutic or prophylactic immune response against an antigen.

The specification does not enabled one of skill to use the method claimed to induce a therapeutic or prophylactic immune response against an antigen.

It was known in the art at the time of filing that the combination of vector, promoter, antigen, target tissue, level of expression and route of administration required to target the desired tissue and obtain a therapeutic or prophylactic effect using gene therapy was unpredictable (Miller, 1995, FASEB J., Vol. 9, pages 190-199; pg 198, col. 1; Deonarain, 1998, Expert Opin. Ther. Pat., Vol. 8, pages 53-69; pg 53, 1st ¶, pg 65, 1st ¶ under Conclusion; Verma, Sept. 1997, Nature, Vol. 389, pages 239-242; see entire article, pg 240, sentence bridging col. 2-3; Crystal, 1995, Science, Vol. 270, pg 404-410; pg 409, all of record).

It was known in the art that a CTL response against β-gal could be induced upon administering wild-type vaccinia followed by a fowlpox vector encoding β-gal (Wang, 1995, J. Immunol., Vol. 154, pg 4685-4692), or by administering wild-type fowlpox followed by vaccinia virus encoding β-gal (pg 4689, col. 2, last sentence). However, the art did not teach the immune response was therapeutic or prophylactic.

The specification demonstrates administering a vaccinia, fowlpox or plasmid vector encoding β-gal followed by a different boosting vector encoding β-gal and obtaining a CTL response against β-gal as compared to vaccinia followed by vaccinia or fowlpox followed by fowlpox (pg 25, Ex. 2). The specification discusses various viral vectors (pg 9-10) and various antigens (pg 11-13) to treat a variety of diseases including

cancer (pg 11, lines 11-35). Example 1 teaches increasing survival of mice having β-gal-expressing tumors using vaccinia followed by fowlpox or fowlpox followed by vaccinia, each of which encode β-gal (page 21; Fig.1) and contemplates administering vectors encoding tumor associated antigens (TAA) against melanoma (example 5). The specification did not teach inducing a therapeutic or prophylactic immune response against an antigen.

The specification does not provide adequate guidance to induce a therapeutic or prophylactic immune response against an antigen because the specification does not correlate β-gal with any other antigen or correlate the immune response obtained using vectors encoding β-gal with the immune response obtained using vectors encoding other antigens such that a therapeutic or prophylactic immune response could be obtained. β-gal tumors do not correlate to tumors having tumor-associated antigens (TAA). β-gal does not correlate to TAA because it is a foreign protein while TAA are self-proteins, because β-gal and TAA known in the art do not have the same epitopes recognized by the immune system, β-gal and TAA have different MHC restriction. The ability of β-gal (a foreign protein) and TAA (a "self" protein) differ. Specifically, the specification does not provide any guidance to treat cancer using MART-1, gp100, TRP-1 or TRP-2 because the specification does not correlate the epitope of β-gal causing an immune response with the epitope of any other antigen that may be therapeutic or prophylactic. The specification does not teach the β-gal epitope recognized by the

immune system has the same amino acid sequence or structure as epitopes of MART-1, gp100, TRP-1 or TRP-2 that are recognized by the immune system. The specification does not teach MART-1, gp100, TRP-1 and TRP-2 are H-2L^d –restricted like β-gal. The specification does not teach that MART-1, gp100, TRP-1 or TRP-2 induce an equivalent immune response as β-gal.

Thus, the specification does not provide adequate guidance for one of skill to administer a vector to a mammal to obtain a therapeutic or prophylactic immune response against an antigen by teaching the level of expression of antigen required to induce the desired immune response, how to target antigen expression to the desired tissue such that the desired immune response is obtained, or by correlating β-gal to tumor antigens such as MART-1, gp100, TRP-1 or TRP-2. Given the state of the art at the time of filing taken with the teachings in the specification, it would require one of skill undue experimentation to determine the dosage, route of administration, vector, promoter, antigens, target tissue or level of antigen expression required to obtain a therapeutic or prophylactic immune response using the claimed invention.

Applicants argue the specification discloses the method claimed can be used to induce a CTL response in a mammal at pg 6, lines 21-23, and 27-33. Applicants point out that the scope of protection sought by the claim should be commensurate in scope of enablement provided by the specification to one skilled in the art. Applicants conclude that the claim language is enabled because it is recited in the specification.

Applicants' argument is not persuasive. While the claim language is found in the specification, the scope of the claim language encompasses therapeutic or prophylactic embodiments. In this case, the specification does not enable the scope of "inducing a CTL response" as claimed because the only purpose for "inducing a CTL response" described in the specification is for therapeutic or prophylactic purposes and because the specification does no overcome the art established unpredictability for one of skill in the art to administer vectors encoding antigens to induce a CTL response that is therapeutic or prophylactic.

The previous rejections of claims 1-8, 21 and 22 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention have been withdrawn in view of the amendments to the claims.

Claims 21 and 22 as newly amended are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The phrase "said antigen encoded by both of the first and second vector" lacks antecedent basis in claim 1, which requires an "antigen against which an immune response is desired."

Claim Rejections - 35 USC ' 103

2. Claims 1-3 and 5-7 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Wang (May 1, 1995, J. Immunol., Vol. 154 (9) 4685-92).

Wang taught administering a wild-type vaccinia virus (VV) to mice followed by administering a fowlpox virus (FPV) encoding β-gal which caused an increase in CTL response in splenocytes as compared to administering wild-type vaccinia followed by vaccinia encoding β-gal (pg 4689, col. 2, Fig. 6, 1st full ¶). The increased CTL response is "an immune response" against the "at least one antigen" as claimed. Wang did not teach administering VV-β-gal followed by administering FPV-β-gal. However, Wang taught a vaccinia VV-β-gal. Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to administer VV-β-gal followed by FPV-β-gal as taught by Wang. One of ordinary skill in the art at the time the invention was made would have been motivated to replace wild-type VV with VV-β-gal to introduce the DNA encoding β-gal sooner thereby inducing the immune response sooner.

Similarly, Wang taught administering a wild-type FPV followed by VV-β-gal, which also caused an immune response (page 4689, col. 2, 1st ¶). Wang did not teach administering FPV-β-gal followed by VV-β-gal. However, Wang taught administering FPV-β-gal caused an immune response. Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to administer FPV-β-gal followed by VV-β-gal. One of ordinary skill in the art at the time the invention was made

to replace wild-type FPV with FPV-β-gal to introduce the DNA encoding β-gal sooner and induce the immune response sooner. Claim 5 is included because VV and FPV encode viral proteins that are recognized as foreign and induce an immune response.

Applicants argue the Office has failed to establish the level of knowledge of the ordinary artisan at the time of filing; therefore, applicants concluded the Office has not provided proof that one of skill would have been motivated to replace wild-type FPV with FPV-β-gal (pg 6 of response). Applicants' argument is not persuasive. Wang represents the knowledge of one of ordinary skill in the art at the time of filing. Wang taught using both VV-β-gal and FPV-β-gal *in vivo.* Wang taught interchanging FPV and VV vectors. Wang also provides evidence that the knowledge of one of ordinary skill in the art at the time of filing included the desire to induce a CTL response in tumors as soon as possible *in vivo* using combinations of FPV and VV vectors to prevent death (see for example Fig. 5). Wang taught administering a wild-type FPV followed by VV-β-gal. Therefore, Wang taught administering two different vectors. Wang taught administering FPV-β-gal followed by FPV-β-gal (Fig. 5C). Therefore, Wang taught administering FPV-β-gal first followed by a second vector encoding β-gal, i.e. pre-immunization with FPV-β-gal. Thus, the motivational statements represent the knowledge of one of ordinary skill in the art at the time of filing found in Wang.

Applicants argue Wang taught away from using rVV on pg 4690, col. 2, 1st ¶ by stating rVV vaccines can cause viremia. Applicants' argument is not persuasive. Wang

still used rVV *in vivo* knowing full well that rVV could cause viremia. Using rVV *in vivo* did not prevent Wang from obtaining a CTL response. The citation by Wang does not "teach away" or prevent one of ordinary skill from using rVV to induce a CTL response *in vivo*.

Applicants argue that a comparison of Fig. 5(B) of Wang and Fig. 1C of the instant application show unexpected results occurred using the claimed method. Specifically, applicants point out that Wang taught that administering rFPV (encoding β-gal) followed by administering rFPV resulted in death by day 22, while administering rFPV followed by rVV resulted in survival for over 110 days (pg 7 of response). Applicants' argument is faulty. Fig 5(B) of Wang represents one administration of rFPV, not two. Fig. 5(C) of Wang taught that after two administrations of rFPV, 13% of the mice survived for 80 days. Survival for one hundred and ten days after two doses of rFPV would not have been unexpected in view of Fig 5(C), especially considering the fact that the second dose given by applicants was on day 17 instead of day 10 as taught by Wang. Applicants' arguments are also not persuasive because applicants have not considered the additive effect of rFPV and rVV in determining the "expected" results.

4. Claims 1-3, 5-7, 21 and 22 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Wang (May 1, 1995, J. Immunol., Vol. 154 (9) 4685-92) for reasons of record.

Wang taught administering VV-β-gal to mice followed by FPV-β-gal or vice versa, which caused an immune response (see 103 rejection above). Wang did not expressly teach replacing β-gal with MART-1 or gp100. However, Wang suggested replacing β-gal with MART-1 and gp100 and taught making FPV-MART-1 and FPV-gp100 (pg 4690, col. 2, last 2 ¶). Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to perform the method of Wang wherein the β-gal gene is replaced with MART-1 or gp100 as suggested by Wang. One of ordinary skill in the art at the time the invention was made would have been motivated to replace β-gal with MART-1 or gp100 to determine if self proteins such as MART-1 or gp100 induced the same immune response as β-gal and to determine if MART-1 or gp100 enhanced the precursor frequency of T-cells that recognize MART-1 or gp100 prior to *ex vivo* expansion (pg 4690, col. 2, ¶ 2, line 4).

Applicants refer to "the arguments above" which have been addressed.

5. Claim 1-8 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Wang (J. Immunol., (1995 May 1) 154 (9) 4685-92) in view of Zhai (Jan. 15, 1996, J. Immunol., Vol. 156, No. 2, pages 700-710).

Wang taught administering VV-β-gal to mice followed by FPV-β-gal, which caused an increase in CTL response in splenocytes as compared to administering two doses of vaccinia virus encoding β-gal. Wang did not teach replacing the vaccinia virus

or fowlpox virus with an adenovirus. However, Zhai taught administering an adenoviral vector encoding β-gal to mice and obtaining an immune response.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to perform the method of Wang wherein the vaccinia virus or fowlpox virus was replaced with the adenoviral vector taught by Zhai. One of ordinary skill in the art at the time the invention was made would have been motivated to replace the vaccinia virus (the first vector) with the adenoviral vector to increase the CTL response against antigen as compared to administering adenoviral vector followed by readministration of adenoviral vector. One of ordinary skill in the art at the time the invention was made would have been motivated to replace the fowlpox virus (the second vector) with the adenoviral vector to determine if fowlpox was the only virus that could be used to obtain a CTL response against antigen after administering vaccinia virus.

Applicants mention the deficiencies of Wang and Zhai but do not provide any specific arguments regarding why the combined teachings of Wang and Zhai do not teach all the limitations of the claims or why motivation is lacking (pg 8 of response). Applicants' argument is not persuasive. The combined teachings of Wang and Zhai taught all the limitations of claim and one of ordinary skill in the art would have been motivated to combine the teachings of Wang and Zhai.

Conclusion

No claim is allowed.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached on Monday through Friday from 9:00 am to 5:30 pm at 571-272-0738.

Questions of a general nature relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-1235.

If attempts to reach the examiner, patent analyst or Group receptionist are unsuccessful, the examiner's supervisor, Amy Nelson, can be reached on 571-272-0804.

The official fax number for this Group is (703) 872-9306.

Michael C. Wilson

MICHAEL WILSON
PRIMARY EXAMINER